DETAILED ACTION

Applicant's remarks and amendment filed on 2/26/2008 are acknowledged. Claims 4, 8, 11, 15, 19, 21, and 24 are amended. Claims 72-75 are added. Claims 1-75 are pending. Claims 23-71 are withdrawn as being drawn to nonelected inventions. Claims 1-22 and 73-75 are currently under examination.

Specification

The objection to the specification for the use of the trademarks ROSETTA, TUNER, and ORIGAMI is maintained for the reasons set forth in the previous rejection.

Applicant argues: that the names of the individual strains in the specification are not trademarks because the terms ROSETTA, TUNER, and ORIGAMI are trademarks used to refer to groups of bacterial strains rather than individual strains.

Applicant's arguments have been fully considered and deemed non-persuasive.

The individual strains include trademarked names which refer to the source of those bacteria. This is somewhat analogous to DR. PEPPER, which is a trademark. There are various flavors, such as Cherry Vanilla DR. PEPPER or Diet DR. PEPPER. The cherry vanilla version still contains a trademark that refers to the source of the product, whether or not the cherry vanilla portion of the name is trademarked. In the instant case, the term objected to identify the source of certain strains of bacteria and the characteristics of the bacteria can be changed by the manufacturer at any time. The trademarks should be accompanied by generic terminology describing the trademarked product (for example, ORIGAMI host strains are K-12 derivatives that have mutations in both the thioredoxin reductase and glutathione reductase genes). It is noted that said terminology must have support as of the filing date in order to avoid new matter issues.

Claim Objections Withdrawn

The objection to claims 5 and 16 under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim is withdrawn in light of applicant's arguments.

New Claim Objections

Claims 10-11, 21-22, and 72-75 are objected to because of the following informalities: the claims refer to E. coli. It is customary for scientific names to be italicized or underlined. Appropriate correction is required.

Claim Rejections Withdrawn

The rejection of claims 1-8 and 12-19 under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter, is withdrawn in light of applicant's arguments.

The rejection of claims 8 and 19 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, is withdrawn in light of applicant's arguments.

The rejection of claims 4, 6, 8, 11, 15, 17, 19, and 22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The rejection of claims 4 and 15 under 35 U.S.C. 112, second paragraph, as being rendered vague and indefinite by the phrase "wherein the cysteine at amino acid residue 192 of the mature SpeB polypeptide is substituted by a serine," is withdrawn in light of applicant's amendment thereto.

The rejection of claims 6 and 19 under 35 U.S.C. 112, second paragraph, as being rendered vague and indefinite by the phrase "wherein an antibody specific for the mature SpeB polypeptide cross-reacts with a wild-type SpeB polypeptide and neutralizes SpeB polypeptide activity," is withdrawn in light of applicant's arguments.

The rejection of claims 8 and 19 under 35 U.S.C. 112, second paragraph, as being rendered vague and indefinite by the use of the terms, "pET, pRSET, pCRT7-CTTOPO, and pIVeX," is withdrawn upon further consideration.

The rejection of claims 12-22 under 35 U.S.C. 103(a) as being unpatentable over Gubba *et al.* (Infect. Immun., 66:765-770, 1998, ID filed 1/9/2006) in view of Matsuka *et al.* (Infect. Immun., 67:4326-4333, 1999), is withdrawn. Applicant correctly points out that, while it was known that pro-SpeB was necessary for solubility of mature SpeB, this was seen only in the context of a single full-length chain and not with separate proteins. The ability of pro-SpeB to promote solubility of mature SpeB through intermolecular interactions was not known in the art.

The rejection of claims 1-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gubba *et al.* (Infect. Immun., 66:765-770, 1998, ID filed 1/9/2006) and Matsuka *et al.* (Infect. Immun., 67:4326-4333, 1999) as applied to claims 12-22 above, and further in view of Tan (Prot. Expression and Purification, 21:224-234, 2001), is withdrawn. Applicant correctly points out that, while it was known that pro-SpeB was necessary for solubility of mature SpeB, this was seen only in the context of a single full-length chain and not with separate proteins. The ability of pro-SpeB to promote solubility of mature SpeB through intermolecular interactions was not known in the art.

Claim Rejections Maintained

35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The rejection of claims 6 and 17 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, is maintained for the reasons set forth in the previous office action.

Applicant argues:

1. That the specification describes an actual reduction to practice of the claimed invention.

2. That identification of immunoepitopes is not required to claim antibodies to an antigen. Applicant asserts that, because they have disclosed an antigen (mature SpeB

polypeptide), the disclosure provides sufficient support for claims directed to antibodies reactive against that SpeB polypeptide.

3. The specification discloses a particular sequence and assay for functionality. Applicant asserts that the present case is analogous to Example 14 of the Written Description Guidelines. Applicant argues that Example 14 teaches that when an application describes a particular sequence and an assay for determining functionality, the application contains sufficient written description for claims directed to the sequence itself as well as variants thereof that have a degree of homology and that maintain functionality. Applicant contends that in the instant case, they have disclosed a sequence (mature SpeB polypeptide) and an assay for determining functionality of that sequence (as shown in Example 6).

Applicant's arguments have been fully considered and deemed non-persuasive.

Regarding argument 1, applicant correctly points out that an actual reduction to practice is one way to show possession of an invention, and the embodiments disclosed in Example 6 of the specification (i.e., the method of claims 6 and 17 using SEQ ID NO:2 or the C192S variant thereof) meet the written description requirements. However, as set forth previously, the genus encompassed by the claims is far broader that these two embodiments and is highly variant. The specification and claims do not place any limit on the number of changes that can be made to the SpeB polypeptide, does not disclose any correlation between the structure and variants of SEQ ID NO:2 or any correlation of structure with variant function. It is noted that the function required in these claims is not the protease activity of SpeB, but rather is the ability to elicit antibodies that bind to the variant as well as wild-type SpeB and to neutralize SpeB activity.

Regarding argument 2, applicant is correct in pointing out that the identification of immunoepitopes is not required to claim antibodies that bind to a given antigen, so long as said antigen is sufficiently described. The specification discloses two antigens, SpeB with the sequence of SEQ ID NO:2 and the C192S variant of SEQ ID NO:2. However, the instant claims are not drawn to antibodies that bind to either of these. The claims are drawn to a method of producing any SpeB protein (with an undefined number of changes) that elicits antibodies that bind to the variant SpeB as well as to the wild-type SpeB and which neutralize SpeB activity. This is not the same as claiming antibodies that bind to a disclosed antigen.

Regarding argument 3, the written description guidelines to which applicant is referring are not the current written description guidelines, although Example 11 from the new guidelines is applicable. The current Example 11 is comparable to the previous Example 14 and refers to proteins with a given percent identity. The important point of Example 11 is that there must be a disclosed (or art-recognized) correlation between structure and function for undisclosed variants to be sufficiently described. As set forth previously, the art shows that structure is not a reliable indicator of function in the generation of antibodies and applicant has shown no structure other than SEQ ID NO:2 or the C192S variant thereof that have the required activity. While applicant has disclosed *a* sequence and an assay for determining functionality of that sequence, they have not shown that *any* given SpeB polypeptide is capable of generating antibodies that bind to both the variant SpeB and the wild-type SpeB as well as which are capable of neutralizing SpeB function.

As outlined previously, the claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to a vast genus of methods for expressing a mature SpeB polypeptide, wherein the mature SpeB polypeptide binds and is neutralized by antibodies that are cross-reactive with wild-type SpeB polypeptide. To fulfill the written description requirements set forth under 35 USC § 112, first paragraph, the specification must describe at least a substantial number of the members of the claimed genus, or alternatively describe a representative member of the claimed genus, which shares a particularly defining feature common to at least a substantial number of the members of the claimed genus, which would enable the skilled artisan to immediately recognize and distinguish its members from others, so as to reasonably convey to the skilled artisan that Applicant has possession the claimed invention. To adequately describe the genus of methods for expressing a mature SpeB polypeptide, wherein the mature SpeB polypeptide binds and is neutralized by antibodies that are cross-reactive with wild-type SpeB polypeptide, applicant must adequately describe the antigenic determinants (immunoepitopes) that elicit the required cross-reactive and neutralizing antibodies directed against SpeB polypeptides.

The specification, however, does not disclose distinguishing and identifying features of a

representative number of members of the genus of immunogenic polypeptides to which the claims are drawn, such as a correlation between the structure of the immunoepitope and its recited function (to elicit the required cross-reactive and neutralizing antibodies directed against SpeB polypeptides), so that the skilled artisan could immediately envision, or recognize at least a substantial number of members of the claimed genus of immunogenic compositions. Moreover, the specification fails to disclose which amino acid residues are essential to the function of the immunoepitope or which amino acids might be replaced so that the resultant immunoepitope retains the activity of its parent, or by which other amino acids the essential amino acids might be replaced so that the resultant immunoepitope retains the activity of its parent. Therefore, since the specification fails to adequately describe at least a substantial number of members of the genus of immunoepitopes to which the claims are based; the specification fails to adequately describe at least a substantial number of members of the claimed genus of methods for expressing a mature SpeB polypeptide, wherein the mature SpeB polypeptide binds and is neutralized by antibodies that are cross-reactive with wild-type SpeB polypeptide.

MPEP § 2163.02 states, "[a]n objective standard for determining compliance with the written description requirement is, 'does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed' ". The courts have decided:

> The purpose of the "written description" requirement is broader than to merely explain how to "make and use"; the applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the "written description" inquiry, *whatever is now claimed.*

See *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Federal Circuit, 1991). Furthermore, the written description provision of 35 USC § 112 is severable from its enablement provision; and adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Ltd.,* 18 USPQ2d 1016.

The Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, paragraph 1, ``Written Description" Requirement (66 FR 1099-1111, January 5, 2001) state,

"[p]ossession may be shown in a variety of ways including description of an actual reduction to practice, or by showing the invention was 'ready for patenting' such as by disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention" (*Id.* at 1104).

The *Guidelines* further state, "[f]or inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species *cannot* be achieved by disclosing only one species within the genus" (Id. at 1106); accordingly, it follows that an adequate written description of a genus cannot be achieved in the absence of a disclosure of at least one species within the genus. As evidenced by Greenspan *et al.* (Nature Biotechnol. 7: 936-937, 1999), defining epitopes is not as easy as it seems. Greenspan *et al.* recommends defining an epitope by the structural characterization of the molecular interface between the antigen and the antibody is necessary to define an "epitope" (page 937, column 2). According to Greenspan *et al.*, an epitope will include residues that make contacts with a ligand, here the antibody, but are energetically neutral, or even destabilizing to binding. Furthermore, an epitope will not include any residue not contacted by the antibody, even though substitution of such a residue might profoundly affect binding. Accordingly, it follows that the immunoepitopes that can elicit a protective immune response to a given pathogen can only be identified empirically. Therefore, absent a detailed and particular description of a representative number, or at least a substantial number of the members of the genus of immunoepitopes, the skilled artisan could not immediately recognize or distinguish members of the claimed genus of methods for expressing a mature SpeB polypeptide, wherein the mature SpeB polypeptide binds and is neutralized by antibodies that are cross-reactive with wild-type SpeB polypeptide. Therefore, because the art is unpredictable, in accordance with the *Guidelines*, the description of immunoepitopes (antigenic determinants) is not deemed representative of the genus to which the claims refer. Hence, the claims do not meet the written description requirements.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

The rejection of claims 11 and 22 under 35 U.S.C. 112, second paragraph, as being indefinite because they contain the trademarks/trade names ROSETTA, TUNER, and ORIGAMI, is maintained for the reasons set forth in the previous office action.

Applicant argues: That the strain identifiers used in the claims are not trademarks. Applicant asserts that the trademarks ROSETTA, TUNER, and ORIGAMI are trademarks that refer to groups of strains, but the individual strain identifiers are not trademarks. Applicant argues that the individual strain identifiers are "names used in trade" which are permitted in patent claims. Applicant argues that the lineage and genetic characteristics of each strain are fully defined in the literature, and offers a Novagen 2004/2005 catalog as evidence of this. Applicant further asserts that the defined lineage and genetic characteristics identify a single article or product irrespective of producer, making these names used in trade.

Applicant's arguments have been fully considered and deemed non-persuasive.

The individual strain identifiers include trademarks that identify the source of the goods. The fact that there are multiple versions of a given trademark (e.g. ORIGAMI(DE3)pLysE or ORIGAMI(DE3)pLacI) does not negate the fact that ORIGAMI is a trademark identifying the source of that strain. A "name used in trade" is a nonproprietary name. Despite applicant's assertions, the names ROSETTA, TUNER, and ORIGAMI are proprietary names with identify products made by a specific manufacturer. As such, the manufacturer is free to change these products at any time. This is the reason the scope of the claims is uncertain. The fact that literature can be found that describes these products does not mean that they are nonproprietary names. It is also noted that the catalog used by applicant to describe said strains was published after the filing of the instant application and provides no indication of what the claimed products were at the time of filing. Finally, trademarks must be capitalized.

As outlined previously, where a trademark or trade name is used in a claim as a limitation to identify or describe a particular material or product, the claim does not comply with the requirements of 35 U.S.C. 112, second paragraph. See *Ex parte Simpson*, 218 USPQ 1020 (Bd. App. 1982). The claim scope is uncertain since the trademark or trade name cannot be used properly to identify any particular material or product. A trademark or trade name is used to identify a source of goods, and not the goods themselves. Thus, a trademark or trade name does not identify or describe the goods associated with the trademark or trade name. In the present

case, the trademarks/trade names are used to identify/describe specific *E. coli* strains and, accordingly, the identification/description is indefinite.

New Claim Rejections

35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 8, 11, 22, and 72-75 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Regarding claims 8, 11, 19, and 22, applicant has amended these claims to recite "and mixtures thereof." This phrase does not appear in the specification or original claims as filed. Applicant points to page 4 of the instant specification to support this amendment; however, there is not mention of mixtures of these plasmids or strains in the specification. Therefore, this limitation is new matter.

Regarding claim 72 (and dependent claim 73), the new claim includes the limitation "wherein the E. coli strain is a derivative of BL21 or K-12." Applicant refers to several original claims and pages in the specification to support the new claim. However, the specification and original claims only disclose specific BL21 strains (e.g. BL21(DE3) or ORIGAMIB(DE3)) and do not disclose BL21 strains in general or derivatives of BL21 other than those specifically listed in the specification. The specification does disclose K12 strains in general and discloses several specific K12 derivatives (e.g. ORIGAMI strains), but does not disclose any K12 derivatives other than those specifically listed in the specification. Therefore, this limitation is new matter.

Regarding claim 74 (and dependent claim 75), the new claim includes the limitation "wherein the E. coli strain is BL21, K-12, or mixtures thereof." Applicant refers to several

original claims and pages in the specification to support the new claim. However, the specification and original claims only disclose specific BL21 strains (e.g. BL21(DE3) or ORIGAMIB(DE3)) and do not disclose BL21 strains in general. In addition, the neither the specification nor the original claims disclose mixtures of BL21 and K-12 strains. Therefore, this limitation is new matter.

Regarding claims 73 and 75, the new claims include a list of characteristics (or combinations thereof) that the E. coli cell must have. Applicant refers to several original claims and pages in the specification to support the new claim. The specification and original claims disclose specific strains that inherently have various combinations of these characteristics. For example, ORIGAMI(DE3) has characteristics iv and v. While the specifically disclosed strains have various combinations of these characteristics, this does not provide support for *any E. coli* BL21 or K-12 strain having *any* combination of these characteristics. Therefore, this limitation is new matter.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 11, 22, and 74-75 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 11 and 22 are rendered vague and indefinite by the phrase "and mixtures thereof." It is not clear how a bacterial strain can be a mixture of strains. A bacterial strain may have a mixture of characteristics from various strains, but a single strain cannot be a mixture of strains.

Claim 74 (and dependent claim 75) is rendered vague and indefinite by the phrase "or mixtures thereof." It is not clear how a bacterial strain can be a mixture of strains. A bacterial strain may have a mixture of characteristics from various strains, but a single strain cannot be a mixture of strains.

Conclusion

Claims 1-5, 7, 9, 12-16, and 18-20 are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian J. Gangle whose telephone number is (571)272-1181. The examiner can normally be reached on M-F 7-3:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shanon Foley can be reached on 571-272-0898. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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